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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,049	11/01/2005	Eva Kontsekova	SONN:066US	5434

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EXAMINER

LEAVITT, MARIA GOMEZ

ART UNIT	PAPER NUMBER
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1633

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/521,049

Applicant(s)

KONTSEKOVA ET AL.

Examiner

Maria Leavitt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09-17-2007 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 17-37 are pending. Claims 34-37 have been added by Applicants amendment filed on 09-17-2007. Currently, claims 17-37 are pending for examination.
3. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 filed on 09-17-2007, however the declaration was unexecuted by Dr. Peter Filipcik; therefore, it has not been considered.

Remaining objections/ rejections in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112 – enablement

The examiner recognizes that an error was inadvertently made in the previous office

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action in view of the previous Declaration under 37 C.F.R. § 1.132 signed by Dr. Peter Filipcik teaching the generation of the transgenic rat line #318 which is the same transgenic rat disclosed in the as- filed specification (page 22, paragraph 2) and the characterization of said transgenic rat # 318 phenotype in the post filling publication by Zilka et al., (2006, FEBS Letters 580:3582-3588) filed on 01-10-2007, as exhibit 2. Therefore the scope of enablement of the instant claims have been modified to SEQ ID No. 3, which correspond to nucleotides 277-999 encoding amino acids 93-333 (Fig. 1 of the as-filed specification).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-33 remain rejected and claims 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic rat whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID No. 3, said DNA operably linked to a promoter, wherein the promoter is a mouse Thy-1 promoter, wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology occurs in the rat when compared to normal rats,

does not reasonably provide enablement for any non-human transgenic animal which comprises a DNA construct comprising a genus of cDNA molecules coding for N- and C-terminally truncated tau molecules wherein the cDNA has truncated at least 30 nucleotides downstream of the start codon and truncated at least 30 nucleotides upstream of the stop codon of the full length tau cDNA. Moreover, the instant claims do not provide sufficient enablement for any promoter (e.g., constitutive or tissue specific) other than the Thy-1 promoter for the observed phenotype of neurofibrillary pathology in rat brain.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims

As stated in the previous office action, at the effective filing date of the present application (07/09/2003), the transgenic art was and continues to be unpredictable with respect to the generation of any transgenic animal and transgene behavior *in vivo*. Transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) (Sanders Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2). For example, Moreadith et al., (1997, J Mol Med pp. 208-216) teaches that several putative ES cells lines have been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but the technology was limited to mice (page 214, col. 1, paragraph 3, lines 5-12). Post filing art by Keefer et al., (2004,

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Animal Reproduction Science, pp. 5-12) brings similar insight into the lack of predictability of generating any transgenic animal as the author recognizes the inefficiency of pronuclear microinjection in transgenic techniques and the unpredictability of transgene expression when applied to generating cows, goats and sheeps (p.6, last paragraph bridging to p. 7, paragraph 1). Moreover, Sigmund (Arterioscler Thromb Vasc Biol, 2000, pp. 1425- 1429) corroborates the lack of predictability of phenotypes in transgenic models when he discloses that the phenotype caused by a specific genetic modification is strongly influenced by genes unlinked to the targeted locus. Sigmund (Arterioscler Thromb Vasc Biol, 2000, p. 1425, col. 1, paragraph 2) teaches that even strain differences between mice carrying the same construct can profoundly influence the phenotype. Thus, the art of record does not provide enablement for the claimed invention of making and using any transgenic animal other than a transgenic rat whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID No. 3 exhibiting of neurofibrillary pathology in the brain. Thus at the time of the instant invention, the skilled artisan would have needed to engage in an undue amount of experimentation to implement the claimed invention without a predictable degree of success.

With regard to claimed embodiments directed to a transgenic non-human animal comprising a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, said construct comprising a minimally truncated tau core of SEQ ID No. 9, there is a high degree of unpredictability associated with the making and using of such embodiments. The instant specification fails to teach which specific amino acids to be substituted, deleted or inserted within the minimally truncated tau core, at which positions and in which combinations such that

the encoded polypeptide derivative for N- and C-terminally truncated tau gene is still functional to yield results contemplated by Applicant. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein one specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Similarly, in discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study (Page 6, Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Post filing art teaches that even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). Though the recombinant technology for the generation of new mutant proteins is highly developed, the ability to determine *a priori* whether a mutation and/or deletion and/or insertion will generate a functional protein is not predictable. Since the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to determine alternative sequences of N- and C-terminally truncated tau protein molecules comprising a minimally truncated tau core of SEQ ID No. 9. This disclosure is limited to the DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID No. 3.

In so far as the expression of a transgene, it was also well known in the art at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the

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gene to a promoter that controls gene expression (Kappel, Current Biology, 1992, entire document, specifically, p. 349, col. 2 paragraph 1). Additionally, it was well known in the art that not all promoters result in efficient expression or expression at levels in the appropriate tissues to result in a phenotype that is useful (Williams et al., (J. Appl. Physiol., 2000, p. 1124, col.2, lines 15-19). Logan et al., (1999, Clinical and Experimental Pharmacology and Physiology, p. 1021, col. 2, paragraph 2) further corroborates that the challenge in the development of transgenic animals is not in the process, but the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level. Therefore, it is clearly set forth in the art the required linkage of a gene to a promoter and selection of tissue specific promoters for effective expression of a gene of interest in tissue specific manner. Thus it would require undue experimentation for the skilled artisan to express the truncated Tau protein exhibiting neurofibrillary pathology in rat brain other than with a with the brain-specific genes encoding thy-1 promoter.

Reply to applicant arguments as they relate to rejection of Claims 17-37 under 35

U.S.C. 112, first paragraph, scope of enablement.

On pages 7 and 8 of applicants' remarks, in relation of enablement for the use of any promoter for the instantly claimed invention, Applicants argue that there is sufficient disclosure for the teaching of a recombinant nucleic acid sequence operably linked to tissue specific or general promoter for the purpose of expression of said sequence in mammalian cells. Moreover, Applicants contend that "in light of the specification, a person of ordinary skill in the art would understand that a "DNA construct" as recited in claim 17 contains a promoter operably linked to the cDNA molecule coding for N- and C- terminally truncated tau molecules". Further,

Applicants cite on page 9 promoters such as the CMV promoter that have been used to drive the expression of several different transgenes in the central nervous system of rat, mice and monkeys". As such, Applicants contend, the scope of promoters encompassed by the current claims is enable by the specification. Such is not persuasive

As an initial matter, the Examiner notices that the numerous references cited by applicants in pages 9-15 of Applicants arguments and remarks filed on 09-17-2007, have not been provided. Therefore, the arguments in relation to said references are not found persuasive, as the documents have not been filed. Moreover, in relation to the requirement of a DNA construct operably linked to a promoter to control gene expression, the instant claims broadly embrace expression of a DNA construct encoding a N- and C-terminally truncated human tau protein in the rat brain so as to exhibit neurofibrillary pathology when compared to normal rats, without requiring the DNA to be operably linked to a promoter. As discussed in the paragraph above, the state of the art at the time of filing require for a gene to be operably linked to a promoter for expression of said gene of interest in a transgenic animal. Thus it would require undue experimentation for one of skill in the art to express a gene that is not necessary linked to a promoter as encompassed by the instant claims. Moreover, the art teaches that specific promoters are necessary for in efficient expression or expression at levels in the appropriate tissues to result in a phenotype that is useful. Considering the unpredictability of the technology, it is unreasonable to infer that the use of a CMV promoter which is active in a wide range of tissues and drives high-level constitutive expression will generate a transgenic non-human animal exhibiting the same neurofibrillary pathology as the claimed invention when expressed in

brain cells of animals. Indeed, the global expression of a truncated tau gene under the control a CMV promoter will necessarily result in a different transgene phenotype.

In relation to the use of any transgenic animal other than rat, Applicants argue at pages 13-14, that a variety of animal models including hamsters, rabbits and others have been used as suitable models for Alzheimer's disease. As such, Applicants contend, the claims are enable for non-human transgenic animal models and "the evidence demonstrates that such animal exhibit characteristics that make them suitable models for Alzheimer's disease.

The examiner notices that the references cited by applicants in pages 12-14 of Applicants arguments and remarks filed on 09-17-2007, have not been provided. Therefore, in the absence of evidences applicant arguments are merely assertions that cannot take the place of evidence already of record. Moreover, it is noticed that post-filing date references cited by Applicants do not remedy the insufficient guidance of the specification for a skilled artisan to reasonably enable the claimed invention unless later-dated references provide evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. Therefore, claims drawn to any non-transgenic-human animal comprising a construct expressing a truncated tau protein as embraced by the claims fails to correlate with the scope of enabling disclosure set forth in the specification.

At pages 12-13 of Remarks, in relation to the correlation between expression of any derivative of the Alzheimer's tau proteins in rat with a useful phenotype other than neurofibrillary pathology, Applicants argue that "the transgenic animals encompassed by the current claims are useful models of Alzheimer's disease because they exhibit the most important

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and earliest immunohistochemical finding in Alzheimer's disease (i. e., neurofibrillary pathology) and they exhibit other pathological features associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes (Filipcik Declaration, para. 11)". Such is not persuasive.

The examiner notices that the references cited by applicants in pages 12-13 of Applicants remarks filed on 09-17-2007, have not been provided. Therefore, in the absence of evidences applicant arguments are merely assertions that cannot take the place of evidence. Moreover, it is noticed that post-filing date references cited by Applicants (e.g., Braak et al., 2006, Cente et al., 2006) do not remedy the insufficient guidance of the specification for a skilled artisan to reasonably enable the claimed invention unless later-dated references provide evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. Therefore, the instant claims drawn to any non-transgenic-human animal comprising a construct expressing a truncated tau protein as embraced by the claims as useful models for any Alzheimer's pathology including hypertension, diabetes, hypercholesterolemia, and a variety of neurobehavioral symptoms fails to correlate with the scope of enabling disclosure set forth in the specification at the effective filing date.

At page 14 of Applicants remarks, Applicants argue "the Action alleges that the Hrnkova reference teaches a lack of nexus between transgenic rats with human truncated tau protein and any Alzheimer's disease. There is, however, no basis for such an allegation. The Hrnkova reference only serves to further demonstrate the usefulness of a transgenic animal encompassed by the current claims as a model for NF pathology and Alzheimer's disease" [emphasis added]. Such is not persuasive.

The examiner notices that the Hrnkova reference is post filing art; therefore, to enable the claimed invention, the teachings the Hrnkova reference must provide evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. Additionally, though the Hrnkova reference teach at paragraph bridging pages 206-207, "rat transgenic expression of human truncated tau, derived from sporadic Alzheimer's disease, led to the development of AD tau cascade. The cascade was represented by extensive neurofibrillary pathology satisfying several histopathological and biochemical criteria used for identification of neurofibrillary degeneration in AD", the publication is silent about how the phenotype observed in rats including neurodegeneration by expression of human truncated tau leading to progressive neurobehavioral impairments correlates to treatment prevention and/ or diagnosis of Alzheimer's pathologies in humans. In other words, are the gene mutations in humans resulting in Alzheimer's pathologies the same as in the transgenic truncated tau protein model? At the effective filing date of the present application, the prior art (see art of record discussed in the action mailed on 04-17-2007, pp. 7-8), did not provide such guidance, thus it is incumbent upon the instant specification to do so. In the absence of such guidance provided by the instant specification and given the state and unpredictability of the relevant art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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